PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JPP284	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/GB2004/002867	International filing date *(day/month/year)* 02.07.2004	Priority date *(day/month/year)* 04.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/7052		
Applicant EL-REFAEY Hazem		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 10 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the International application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.05.2005	12.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Bonzano, C Telephone No. +31 70 340-2202

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002867

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-15 as originally filed

   Claims, Numbers

   1-21 received on 04.05.2005 with letter of 03.05.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 6 (partially)
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

   * *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002867

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 3-5 (partially); 2,6-10,15-21; 11-14 (with regard to industrial applicability)

because:

☒ the said international application, or the said claims Nos. 11-14 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 3-5 (partially); 2,6-10,15-21

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 3-5 (partially); 1,11-14 .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4,12,14
	No:	Claims	1,5,11,13
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1,3-5,11-14
Industrial applicability (IA)	Yes:	Claims	1,3-5
	No:	Claims	11-14

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item I

1. The attention of the applicant is drawn to the fact that amended claim 6 is not acceptable under Article 19(2)PCT, because the application as originally filed only discloses combinations of azithromycin with prostaglandin: only (a) an antibiotic, (b) a prostaglandin and optionally (c) instructions for the simultaneous, sequential or separate administration are disclosed in the original application. Therefore combinations including also an analgesic or a NSAID etc., as in present claim 6, are not acceptable under Article 19(2) PCT and Article 34(2)b PCT. Claim 6 has been considered as if it had not been amended.

Re Item III

2. Concerning the first invention, the subject matter of claims 11-14 concerns a method of treatment of the human/animal body which is considered by this Autorithy to be covered by the provisions of Rule 67.1 (IV) PCT. Consequently, no report will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4) (a)(I)PCT).

Re Item IV.

1. The separate inventions/groups of inventions are:

1) 3-5, (partially); 1,11-14

Use of a medicament for vaginal and/or rectal administration, comprising azithromycin, optionally further comprising metronidazole, for treating pelvic tissue infection.

2) 2-5 (partially)

Use of a medicament for vaginal and/or rectal administration, comprising azithromycin, with an analgesic, optionally further comprising metronidazole, for treating pelvic tissue infections.

3) 2-5 (partially)

Use of a medicament for vaginal and/or rectal administration, comprising azithromycin, with a NSAID, optionally further comprising metronidazole, for treating pelvic tissue infection.

4) 2-5 (partially)

Use of a medicament for vaginal and/or rectal administration, comprising azithromycin, with a local anaesthetic drug, optionally further comprising metronidazole, for treating pelvic tissue infection.

5) 2-5 (partially)
Use of a medicament for vaginal and/or rectal administration, comprising azithromycin, with:

1. an analgesic,
2. a NSAID,
3. and/or a local anaesthetic drug,

optionally further comprising metronidazole, for treating pelvic tissue infection.

6) 6-10
Use of a medicament for vaginal and/or rectal administration comprising azithromycin, with a prostaglandine, in particular misoprostol, optionally with cervagem, for treating pelvic tissue infection.

7) 15-21
Use of a medicament for vaginal and/or rectal administration for reducing surgical trauma resulting from gynaecological operation, comprising an antibiotic, in particular azithromycin, with a prostaglandine, in particular misoprostol, optionally with cervagem, or metronidazol.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons.
The problem to be solved by the present invention is to provide a medicament for use by vaginal and/or rectal administration:
1. for treating pelvic tissue infection
2. for reducing surgical trauma resulting from gynaecological operation.
The proposed solution to the problem 1. is to use a composition for vaginal and rectal administration comprising:
1. azithromycin, alone or optionally with:
2. an analgesic,
3. a NSAID,
4. a local anaesthetic drug,
5. an analgesic, a NSAID and a local anaesthetic drug
6. a prostaglandine, in particular misoprostol, optionally with cervagem.
The proposed solution to the problem 2, is to use a composition for vaginal administration comprising azithromycin and a prostaglandine, optionally with misoprostol, optionally with cervagem.

The activity as antibiotic represents the technical feature common to the different compositions claimed.

Document WO 03/039559 (D1) discloses vaginal and rectal tablets and suppositories comprising azithromycin for treating fungal and bacterial infections of the vaginal cavity (see page 29, example I.4; page 7, paragraph 2; table X). The vaginal cavity is a pelvic organ and falls under the definition of pelvic tissue. Document D2 discloses azithromycin vaginal effervescent tablets for treating gonorrhea and vaginitis and cervicitis, which are pelvic tissue infections.

The attention of the applicant is drawn to the fact that the use of a compound for the manufacture of a medicament for the treatment of a specified disease pelvic tissue infections can only be patented once and cannot be patented again under the guise of another or newly specified pharmacological mechanism. In fact, the discovery of such a new way of action is not an invention under Rule 39.1 (i) PCT, as the technical effect obtained remains the same (treating the same disease). In the present case the discovery of an alternative mechanism of action (accumulation of the compound in the pelvic tissue, achievement of a tissue concentration of 2 mg/kg in endometrium, cervix and fallopian tubes) does not add a new or better technical effect to the known treatments. The technical effect being identical, the use is not changed by the discovery of an alternative mechanism.

Consequently, because pharmaceutical compositions of azithromycin, as claimed, have already been used by vaginal and/or rectal administration, in the treatment of pelvic tissue infections (cervix, endometrium), the activity of azithromycin as antibiotic can no longer serve as a single general inventive concept linking the compositions, which have no other technical feature in common.

Therefore the uses of the compositions comprising:

1. azithromycin, alone, or with:
2. an analgesic,
3. a NSAID,
4. a local anaesthetic drug,
5 an analgesic, a NSAID and a local anaesthetic drug
6. a prostaglandine, in particular misoprostol, optionally with cervagem,

by vaginal and/or rectal administration for treating pelvic tissue infection represent each a distinct invention, characterised by its own special technical features, i.e. the structural features of the compositions.

Moreover, the use of the composition comprising an antibiotic, with a prostaglandine,

optionally with misoprostol, optionally with cervagem by vaginal and/or rectal administration for reducing surgical trauma resulting from gynaecological operation represents a distinct invention, characterised by its own special technical features, i.e. the structural features of the compositions and the different second medical use.
The document cited above does not represent a comprehensive search for the defined inventions and is to be considered in the present context only as part of the prior art pertaining to the general idea underlying the present application.

2. The opinion of the International Search Authority was carried out in respect of subject-matter which is covered by the search report, namely the inventions 1 and 7 (now named inventions 1 and 6). The Applicant was invited to restrict the claims to the first invention or to restrict to inventions 1 and 6 and pay an additional fee for the examination of the invention searched (Article 34(3)a PCT).
As there was no reply from the applicant, the present report will be carried out with respect to the first invention mentioned, namely:
Claims 3-5, (partially); 1,11-14: use of a medicament for vaginal and/or rectal administration, comprising azithromycin, optionally further comprising metronidazole, for treating pelvic tissue infection.

Re Item V

1. The following documents are referred to in this communication:
   - D1 : WO 03/039559 A (DAJKA LEVENTE; LUKACS KAROLY (HU); HEGED &; UDBLAC (HU); HUMAN RT (HU)) 15 May 2003 (2003-05-15)
   - D2 : DATABASE WPI Section Ch, Week 200039 Derwent Publications Ltd., London, GB; Class B03, AN 2000-443089 XP002298745 & CN1242193 A (HUIDA PHARM CO LTD DATONG CITY) 26 January 2000 (2000-01-26)

2. For the assessment of the present claims 11-14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty

3.1 Document D1 discloses vaginal and rectal tablets and suppositories comprising azithromycin for treating fungal and bacterial infections of the vaginal cavity.
Document D2 discloses azithromycin vaginal effervescent tablets for treating gonorrhea and vaginitis and cervicitis, which are pelvic tissue infections.

3.2 The attention of the applicant is drawn to the fact that the use of a compound for the manufacture of a medicament for the treatment of a specified disease pelvic tissue infections can only be patented once and cannot be patented again under the guise of another or newly specified pharmacological mechanism. In fact, the discovery of such a new way of action is not an invention under Rule 39.1 (i) PCT, as the technical effect obtained remains the same (treating the same disease). In the present case the discovery of an alternative mechanism of action (accumulation of the compound in the pelvic tissue, achievement of a tissue concentration of 2 mg/kg in endometrium, cervix and fallopian tubes) does not add a new or better technical effect to the known treatments. The technical effect being identical, the use is not changed by the discovery of an alternative mechanism.
Consequently, pharmaceutical compositions of azithromycin, as claimed, have already been used by vaginal and/or rectal administration, in the treatment of pelvic tissue infections (cervix, endometrium).

The subject-matter of claims 1,5,11,13 is therefore not new over D1,D2 (Article 33(2) PCT).

Inventive step

6. The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1,5,11,13, as far as novel, and 3-4,12,14 does not involve an inventive step.
Document D1 discloses vaginal and rectal tablets and suppositories comprising azithromycin for treating fungal and bacterial infections of the vaginal cavity.
Document D2 discloses azithromycin vaginal effervescent tablets for treating gonorrhea and vaginitis and cervicitis, which are pelvic tissue infections.
The present application differs from D1 and D2 in that azithromicin is administered together with an analgesic or a NSAID.
The problem to be solved is to find an alternative treatment to pelvic tissue infections.
Analgesics and NSAIDs are well known as a coadjuvant for treating infections.

The use of a combination of two or more active compounds having a similar, already known activity, is to be considered as inventive, only if it gives a proven surprising effect.
It is pointed out that no surprising effect has been proven by the Applicant. In the absence of any evidence that the present compositions show either an unexpected high synergetic effect or reduced side-effects, the presence of an inventive step has to be denied.
It would therefore be obvious to the person skilled in the art, to use for treating pelvic tissue infections the compound azithromycin, already known for treating pelvic tissue infections, in combination with analgesics or NSAIDs.

CLAIMS

1. Use of a pharmaceutical composition which comprises azithromycin and a pharmaceutically acceptable carrier or diluent in the manufacture of a medicament for use in the treatment and/or prevention of a pelvic tissue infection by vaginal administration.

2. Use as defined in Claim 1 wherein the composition comprises an analgesic, a non-steroidal anti-inflammatory drug, and/or a local anaesthetic drug.

3. Use as defined in Claim 1 or Claim 2 wherein the pelvic tissue infection is a sexually transmitted infection, preferably chlamydia.

4. Use as defined in any one of the preceding claims wherein the composition comprises metronidazole.

5. Use as defined in any one of the preceding claims wherein the composition is for use in the treatment of a cervix, endometrium, fallopian tube and/or parametrium.

6. Use as defined in any one of the preceding claims wherein composition comprises a prostaglandin.

7. Use as defined in Claim 6 wherein the prostaglandin is misoprostol, optionally with cervagem.

8. Use as defined in Claim 1 wherein the composition is provided in the form of a kit comprising

(a) azithromycin and a pharmaceutically acceptable carrier or diluent,

(b) a prostaglandin and

(c) instructions for the simultaneous, sequential or separate administration of (a) and (b) to a patient in need thereof.

9. Use as defined in Claim 8 wherein the medicament is also for use in reducing surgical trauma resulting from a gynaecological operation.

10. Use as defined in Claim 8 or Claim 9 wherein part (b) of the kit comprises a pharmaceutically acceptable carrier or diluent.

11. A method of treating and/or preventing a pelvic tissue infection which method comprises administering vaginally or rectally a therapeutically effective amount of azithromycin to a patient in need of such treatment.

12. A method as defined in Claim 11 wherein the azithromycin is administered with metronidazole.

13. A method as defined in Claim 11 or Claim 12 wherein the infected tissue is a cervix, endometrium, fallopian tube and/or parametrium.

14. A method as defined in any one of Claims 11 to 13 wherein the pelvic tissue infection is a sexually transmitted infection, preferably chlamydia.

15. A method of reducing surgical trauma resulting from a gynaecological operation which method comprises administering vaginally or rectally a composition comprising a therapeutically effective amount of an antibiotic and of a prostaglandin to a patient in need of such treatment.

16. A method as defined in Claim 15 which comprises administering the composition to a patient about to undergo a gynaecological operation.

17. A method as defined in Claim 16 wherein the operation includes a surgical or medical abortion, uterine evacuation of a failed pregnancy and/or a transcervical operation undertaken outside pregnancy.

18. A method as defined in any one of Claims 15 to 17 wherein the composition comprises a pharmaceutically acceptable carrier or diluent.

19. A method as defined in any one of Claims 15 to 18 wherein the prostaglandin is misoprostol, optionally with cervagem.

20. A method as defined in any one of Claims 15 to 19 wherein the antibiotic includes azithromycin, optionally with metronidazole.

21. A method as defined in any one of Claims 15 to 20 wherein the patient is a human or animal patient, especially a human or mammal patient.